

## Non-Technical Abstract

Heart failure from heart attacks or other heart muscle diseases affects millions of people in the United States. Despite recent advances in treatment, the 5-year survival for severely affected individuals remains below 50%. Ventricular assist devices (partial artificial hearts) are used in patients with end-stage heart failure as a bridge to heart transplant. Unfortunately, only a small fraction of patients on assist devices recover sufficiently for the devices to be successfully removed and insufficient donor hearts are available for transplant.

The sarcoplasmic reticulum calcium ATPase 2a (SERCA2a) is a protein that pumps calcium into the storage compartment in heart cells. It is deficient in patients with heart failure. Restoring SERCA2a levels using gene therapy has been shown to improve heart function in animal models of heart failure and strength of contraction in heart cells from people with heart failure. We therefore propose a Phase I trial at two sites (University of Pittsburgh, Massachusetts General Hospital) to test whether expressing SERCA2a using gene therapy in heart failure patients who receive ventricular assist devices in anticipation of heart transplant will be safe. At the time the ventricular assist device is placed, eight patients will receive SERCA2a gene therapy while eight others will receive no active treatment. We will follow the patients for evidence of complications related to the therapy. We will determine whether gene therapy with SERCA2a improves heart function compared to untreated control individuals using echocardiograms (ultrasound) and stress tests. At the time of heart transplant, the native heart will be removed, the amount of extra SERCA2a expression will be determined, and changes in the structure of the heart will be identified.

If successful, this study will be the first human trial of gene therapy for patients with heart failure. It will provide the basis for a novel potential therapy for this devastating illness.